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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,932	04/05/2004	Jonathan Schneck	001107.00466	7013

22907 7590 12/30/2005

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/816,932	SCHNECK ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/5/04 & 11/2/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-23 and 53-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-23 and 53-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/5/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice to Comply with the Sequence Rules.

DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Full compliance with the sequence rules is required in response to this Office Action. A complete response to this Office Action should include both compliance with the sequence rules and a response to the Office Action set forth below. Failure to fully comply with both these requirements in the time period set forth in this Office Action will be held non-responsive.

2. Applicant is required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, in the Brief Description of the Drawings for Figure 1B and Figure 19).

3. Applicant's amendment filed 4/5/04 and Applicant's amendment and response filed 11/2/05 are acknowledged and have been entered.

4. Applicant's petition under 37 CFR 1.84(a) and 1.84(b) to accept color photographs is hereby GRANTED.

5. Applicant's election of Group I (claims 21-23 and newly added claims 53-56), and species of dendritic cell, chimeric protein comprising an HLA-A2 MHC class I molecule and an IgG1 heavy chain comprising a variable region, and the HTLV-1 tax 11-19 peptide in Applicant's said response filed 11/2/05 is acknowledged.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 21-23 and 53-56 read on the elected species.

Accordingly, claims 2, 4 and 13 (non-elected species of Group I) and claims 5-8 and 10-12 (non-elected groups II-IV) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 21-23 and 53-56 are currently being examined.

6. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the Examiner on form PTO-892, they have not been considered.

7. The amendment filed 4/5/04 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the incorporation by reference to application serial nos. 09/789,720 and 09/150,622.

Applicant is required to cancel the new matter in the reply to this Office Action.

8. For the purpose of prior art rejections, the filing date of the instant claims 21-23 and 53-56 is deemed to be the filing date of the 60/082,538 application, *i.e.*, 4/21/98, as the parent applications do not support the claimed limitations of the instant application. The limitation "bound to the surface of a cell" and "wherein the cell is a dendritic cell" does not find support in the 60/058,573 provisional parent application.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 21 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/04314 (IDS reference).

WO 96/04314 teaches an APC transfected with DNA encoding a multivalent fusion, *i.e.,* chimeric, protein comprising two full-length MHC class I molecules (heavy chain and β2m) or MHC class II molecules, each fused to the same antigenic peptide and an immunoglobulin chain, said immunoglobulin chain comprising a constant region, that causes the fusion protein product of the transfected DNA to be expressed on the cell surface, *i.e.,* the chimeric protein is "bound" to the surface of the cell, or can be GPI-linked to the surface of a cell, and use for *in vivo* administration. WO 96/04314 teaches that fusion proteins comprising the MHC class I molecules may comprise an immunoglobulin comprising a variable region. WO 96/04314 teaches the importance of a co-stimulatory molecule in eliciting an MHC class I-restricted CTL response. WO 96/04314 teaches assays to determine if an MHC/peptide combination is stimulating T cells, said assay comprising contacting T cells with APC that expresses the class I MHC complex (especially page 8 at lines 6-24, page 19 at lines 10-17, page 26 at lines 22-30, page 27 at lines 1-30, page 28 at lines 1-16, pages 29-30, paragraph spanning pages 31-32, page 39 at lines 14-21, page 40 at lines 18-27, page 41 at lines 5-15, page 42 at lines 4-16, claims 31 and 31).

11. Claims 21 and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 96/04314 (IDS reference).

WO 96/04314 teaches an APC transfected with DNA encoding a multivalent fusion, *i.e.,* chimeric, protein comprising two full-length MHC class I molecules (heavy chain and β2m) or MHC class II molecules, each fused to the same antigenic peptide and an immunoglobulin chain, said immunoglobulin chain comprising a constant region, that causes the fusion protein product of the transfected DNA to be expressed on the cell surface, *i.e.,* the chimeric protein is "bound" to the surface of the cell, or can be GPI-linked to the surface of a cell, and use for *in vivo* administration. WO 96/04314 teaches that fusion proteins comprising the MHC class I molecules may comprise an immunoglobulin comprising a variable region. WO 96/04314 teaches the importance of a co-stimulatory molecule in eliciting an MHC class I-restricted CTL response. WO 96/04314 teaches assays to determine if an MHC/peptide combination is stimulating T cells, said assay comprising contacting T cells with APC that expresses the class I MHC complex (especially page 8 at lines 6-24, page 19 at lines 10-17, page 26 at lines 22-30, page 27 at lines 1-30, page 28 at lines 1-16, pages 29-30, paragraph spanning pages 31-32, page 39 at lines 14-21, page 40 at lines 18-27, page 41 at lines 5-15, page 42 at lines 4-16, claims 31 and 31).

12. Claims 21 and 23 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 96/04314 (IDS reference).

WO 96/04314 teaches an APC transfected with DNA encoding a multivalent fusion, *i.e.,* chimeric, protein comprising two full-length MHC class I molecules (heavy chain and β2m) or MHC class II molecules, each fused to the same antigenic peptide and an immunoglobulin chain, said immunoglobulin chain comprising a constant region, that causes the fusion protein product of the transfected DNA to be expressed on the cell surface, *i.e.,* the chimeric protein is "bound" to the surface of the cell, or can be GPI-linked to the surface of a cell, and use for *in vivo* administration. WO 96/04314 teaches that fusion proteins comprising the MHC class I molecules may comprise an immunoglobulin comprising a variable region. WO 96/04314 teaches the importance of a co-stimulatory molecule in eliciting an MHC class I-restricted CTL response. WO 96/04314 teaches assays to determine if an MHC/peptide combination is stimulating T cells, said assay comprising contacting T cells with APC that expresses the class I MHC complex (especially page 8 at lines 6-24, page 19 at lines 10-17, page 26 at lines 22-30, page 27 at lines 1-30, page 28 at lines 1-16, pages 29-30, paragraph spanning pages 31-32, page 39 at lines 14-21, page 40 at lines 18-27, page 41 at lines 5-15, page 42 at lines 4-16, claims 31 and 31).

13. Claims 21-23 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,869,270 (IDS reference).

U.S. Patent No. 5,869,270 discloses MHC peptide complex/Ig fusion proteins comprising two MHC class I molecules (heavy chain and β2m), or MHC class II molecules, each fused to the same antigenic peptide and further comprising an immunoglobulin chain, that are expressed on the surface of APC that are dendritic cells by transfection of DNA encoding the said fusion proteins, *i.e.,* the proteins are "bound" to the cells, and the dendritic cells may be used to stimulate an immune response in humans or in animals (especially column 8, column 21 at lines 1-54, column 24, column 25 at lines 1-59).

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 21-23 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/03552 A2 (1/29/98) in view of Celluzzi *et al* (J. Exp. Med. 1/1996, Vol. 183, pages 283-287), Liu *et al* (J.Exp. Med. 1/1997, Vol. 185, No. 1, pages 165-170) and Bendig (Methods: A Companion to Methods in Enzymology, 1995, Vol. 8, pages 83-93).

WO 98/03552 A2 teaches multivalent MHC complex/peptide/IgG fusion proteins, *i.e.,* chimeric proteins, such proteins comprising at least two MHC class I HLA-A molecules attached to a linker, or MHC class II molecules, the linker being IgG1 and each MHC class I molecule bound or fused to an identical peptide. WO 98/03552 A2 further teaches that the linker determines whether the fusion protein will activate or suppress T cells. WO 98/03552 A2 teaches that for enhancing T cell-mediated immunity, the linker will allow delivery of a second, or co-stimulatory signal, this being accomplished by using an IgG that has binding affinity for a cell surface structure on a cell that is capable of delivering a co-stimulatory signal. WO 98/03552 A2 teaches *in vitro* stimulation of T cells using immobilized fusion protein (especially Background and Summary of the Invention, Brief Description of the Drawings for Figure 1, last paragraph on page 2, first two paragraphs on page 3, page 4 at lines 25-26, Figure 1, claims 1-3, 8, 20-23).

WO 98/03552 A2 does not teach wherein the the fusion (or chimeric) protein is bound to a cell, nor wherein the cell is a dendritic cell, nor wherein the cell capable of delivering a co-stimulatory signal is a dendritic cell.

Celluzzi *et al* teach that priming of CTL responses requires the presentation of the relevant antigen by professional antigen presenting cells (APCs) capable of providing co-stimulation, that dendritic cells (DC) are efficient APCs for CTL induction, and that dendritic cells may therefore be an attractive adjuvant for immunizations. Celluzzi *et al* teach that DC pulsed with antigen induce CTL-mediated response to the said antigen (especially first paragraph on page 283), and that such DC is advantageous over other forms of peptide delivery in that the peptide in preformed complexes with class I on the surface of the DC is likely to be presented in the appropriate APC context for T cell stimulation, and that the peptide will be protected from degradation by extracellular proteases (especially last sentence in column 1 on page 286). Celluzzi *et al* teach cell surface antigens on DC, and detection of cell surface antigens using antibodies specific for said cell surface antigens (especially Preparation of DC section at column 2 on page 283).

Liu *et al* teach an IgG1 isotype mouse monoclonal antibody 7D6 specific for the human dendritic cell marker CD21 (especially abstract and Materials and Methods section on page 166 at the second and third full paragraphs at column 1).

Bendig teaches that rodent antibodies may be humanized to avoid adverse immune reactions to rodent sequences when used therapeutically (see entire article).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an MHC class I/peptide/IgG1 fusion protein as taught by WO 98/03552 A2 using a humanized version as taught by Bendig of an IgG1 antibody comprising a variable region specific for a DC cell surface antigen such as taught by Celluzzi *et al* and by Liu *et al*, and to have attached the fusion protein to a cell capable of delivering a co-stimulatory signal as taught by WO 98/03552 A2, said cell being a DC taught by Celluzzi *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to prepare a composition comprising said fusion protein attached to a cell capable of providing a co-stimulatory signal as taught by WO 98/03552 A2 because Celluzzi *et al* teach that DC are capable of providing the requisite co-stimulatory signal, and further teach the advantage of using DC with peptide bound to MHC on their surface for immunization, Liu et al teach a mouse IgG1 antibody to a dendritic cell marker, and Bendig teach humanization of rodent antibodies when used therapeutically in humans. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to do this because Celluzzi *et al* teach that the peptide is likely to be protected from degradation from extracellular proteases while bound to class I, and the construct taught by WO 98/03552 A2 has peptides that are either bound or fused to class I MHC.

16. Claims 21-23 and 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/03552 A2 (1/29/98) in view of Celluzzi *et al* (J. Exp. Med. 1/1996, vol. 183, pages 283-287), Liu *et al* (J.Exp. Med. 1/1997, Vol. 185, No. 1, pages 165-170) and Utz *et al* (J. Virology, 2/1996, Vol. 70, No. 2, pages 843-851).

WO 98/03552 A2 teaches multivalent MHC complex/peptide/IgG fusion proteins, *i.e.,* chimeric proteins, such proteins comprising at least two MHC class I HLA-A molecules attached to a linker, or MHC class II molecules, the linker being IgG1 and each MHC class I molecule bound or fused to an identical peptide. WO 98/03552 A2 further teaches that the linker determines whether the fusion protein will activate or suppress T cells. WO 98/03552 A2 teaches that for enhancing T cell-mediated immunity, the linker will allow delivery of a second, or co-stimulatory signal, this being accomplished by using an IgG that has binding affinity for a cell surface structure on a cell that is capable of delivering a co-stimulatory signal. WO 98/03552 A2 teaches *in vitro* stimulation of T cells using immobilized fusion protein (especially Background and Summary of the Invention, Brief Description of the Drawings for Figure 1, last paragraph on page 2, first two paragraphs on page 3, page 4 at lines 25-26, Figure 1, claims 1-3, 8, 20-23).

WO 98/03552 A2 does not teach wherein the the fusion (or chimeric) protein is bound to a cell, nor wherein the cell is a dendritic cell, nor wherein the cell capable of delivering a co-stimulatory signal is a dendritic cell, nor wherein the MHC molecule is HLA-A2, nor wherein the antigenic peptide is HTLV-1 tax 11-19.

Celluzzi *et al* teach that priming of CTL responses requires the presentation of the relevant antigen by professional antigen presenting cells (APCs) capable of providing co-stimulation, that dendritic cells (DC) are efficient APCs for CTL induction, and that dendritic cells may therefore be an attractive adjuvant for immunizations. Celluzzi *et al* teach that DC pulsed with antigen induce CTL-mediated response to the said antigen (especially first paragraph on page 283), and that such DC is advantageous over other forms of peptide delivery in that the peptide in preformed complexes with class I on the surface of the DC is likely to be presented in the appropriate APC context for T cell stimulation, and that the peptide will be protected from degradation by extracellular proteases (especially last sentence in column 1 on page 286). Celluzzi *et al* teach cell surface antigens on DC, and detection of cell surface antigens using antibodies specific for said cell surface antigens (especially Preparation of DC section at column 2 on page 283).

Liu *et al* teach an IgG1 isotype mouse monoclonal antibody 7D6 specific for the human dendritic cell marker CD21 (especially abstract and Materials and Methods section on page 166 at the second and third full paragraphs at column 1).

Utz et al teach in HLA-A2 positive individuals with HTLV-1 associated HAM/TSP, the vast majority of CD8+ HTLV-1 specific CTL recognize one viral epitope presented by HLA-A2, the immunodominant HTLV-1 tax 11-19 peptide (especially abstract and introduction sections). *Utz et al* teach detecting the presence of such CD8+ T cells using target cells transfected with HLA-A2 and pulsed with the tax 11-19 peptide (especially first section at column 1 on page 8450. *Utz et al* teach that it is not known if the virus-specific CTL are beneficial to the patient or contribute to the pathogenesis of the condition (especially second to last paragraph of article on page 850). *Utz et al* teach generation of the CTL by stimulating CD8+ cells from peripheral blood of patients with antigen pulsed PBL (Materials and Methods section, last paragraph, column 1 on page 844).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an MHC class I/peptide/IgG fusion protein as taught by WO 98/03552 A2 using an IgG1 antibody comprising a variable region specific for a DC cell surface antigen such as taught by Liu *et al*, and to have attached the fusion protein to a cell capable of delivering a co-stimulatory signal as taught by WO 98/03552 A2, said cell being a DC taught by Celluzzi *et al*. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an MHC class I/viral peptide/IgG1 fusion protein using the tax 11-19 peptide and HLA-A2 taught by Utz *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to prepare a composition comprising said fusion protein attached to a cell capable of providing a co-stimulatory signal as taught by WO 98/03552 A2 because Celluzzi *et al* teach that DC are capable of providing the requisite co-stimulatory signal, and further teach the advantage of using DC with peptide bound to MHC on their surface for immunization, Liu et al teach a mouse IgG1 antibody to a dendritic cell marker. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to do this because Celluzzi *et al* teach that the peptide is likely to be protected from degradation from extracellular proteases while bound to class I, and the construct taught by WO 98/03552 A2 has peptides that are either bound or fused to class I MHC. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to prepare a standardized, stable source of APC that provide a strong co-stimulatory signal along with the tax 11-19 peptide bound to HLA-A2 because Utz *et al* teach generation of tax 11-19/HLA-A2 specific CTL from peripheral blood of HTLV-1 patients with HAM/TSP using PBL isolated from HLA-A2 positive patients and pulsed with tax 11-19 immunodominant peptide. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to stimulate and expand CTL *in vitro* for further study since Utz *et al* teach that it is not known if virus-specific CTL are beneficial or deleterious, and the combined references teach *in vitro* stimulation of T cells using immobilized fusion protein.

17. Claims 21-23 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/04314 (IDS reference) in view of Celluzzi *et al* (J. Exp. Med. 1/1996, Vol. 183, pages 283-287), Liu *et al* (J.Exp. Med. 1/1997, Vol. 185, No. 1, pages 165-170) and Bendig (Methods: A Companion to Methods in Enzymology, 1995, Vol. 8, pages 83-93).

WO 96/04314 teaches an APC transfected with DNA encoding a multivalent fusion, *i.e.,* chimeric, protein comprising two full-length MHC class I molecules (heavy chain and β2m) or MHC class II molecules, each fused to the same antigenic peptide and an immunoglobulin chain, said immunoglobulin chain comprising a constant region, that causes the fusion protein product of the transfected DNA to be expressed on the cell surface, *i.e.,* the chimeric protein is "bound" to the surface of the cell, or can be GPI-linked to the surface of a cell, and use for *in vivo* administration. WO 96/04314 teaches that fusion proteins comprising the MHC class I molecules may comprise an immunoglobulin comprising a variable region. WO 96/04314 teaches the importance of a co-stimulatory molecule in eliciting an MHC class I-restricted CTL response. WO 96/04314 teaches assays to determine if an MHC/peptide combination is stimulating T cells, said assay comprising contacting T cells with APC that expresses the class I MHC complex (especially page 8 at lines 6-24, page 19 at lines 10-17, page 26 at lines 22-30, page 27 at lines 1-30, page 28 at lines 1-16, pages 29-30, paragraph spanning pages 31-32, page 39 at lines 14-21, page 40 at lines 18-27, page 41 at lines 5-15, page 42 at lines 4-16, claims 31 and 31).

WO 96/04314 does not teach wherein the cell capable of delivering a co-stimulatory signal is a dendritic cell, nor wherein the said cell is bound to the fusion protein via the variable region of the immunoglobulin portion of the protein.

Celluzzi *et al* teach that priming of CTL responses requires the presentation of the relevant antigen by professional antigen presenting cells (APCs) capable of providing co-stimulation, and that dendritic cells (DC) are efficient APCs for CTL induction and may be an attractive adjuvant for immunizations. Celluzzi *et al* teach that DC pulsed with antigen induce CTL-mediated response to the said antigen (especially first paragraph on page 283), and that such DC is advantageous over other forms of peptide delivery in that the peptide in preformed complexes with class I on the surface of the DC is likely to be presented in the appropriate APC context for T cell stimulation, and that the peptide will be protected from degradation by extracellular proteases (especially last sentence in column 1 on page 286). Celluzzi *et al* teach cell surface antigens on DC and detection of them using antibodies specific for said cell surface antigens (especially Preparation of DC section at column 2 on page 283).

Liu *et al* teach an IgG1 isotype monoclonal antibody 7D6 specific for the human dendritic cell marker CD21 (especially abstract and Materials and Methods section on page 166 at the second and third full paragraphs at column 1).

Bendig teaches that rodent antibodies may be humanized to avoid adverse immune reactions to rodent sequences when used therapeutically (see entire article).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an MHC class I/peptide/IgG fusion protein as taught by WO 96/04314 using a humanized version of an IgG antibody comprising a variable region specific for a DC cell surface antigen such as taught by Celluzzi *et al* or of an IgG1 antibody as taught by Liu *et al*, and to have attached the fusion protein to a cell capable of delivering a co-stimulatory signal as taught by WO 96/04314, said cell being a DC taught by Celluzzi *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to prepare a composition comprising said fusion protein attached to a cell capable of providing a co-stimulatory signal as taught by WO 96/04314 because Celluzzi *et al* teach that DC are capable of providing the requisite co-stimulatory signal, and further teach the advantage of using DC with peptide bound to MHC on their surface for immunization, Liu *et al* teach a mouse IgG1 antibody specific for dendritic cells and Bendig teach the advantage of humanization of rodent antibodies for therapeutic administration. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to do this because Celluzzi *et al* teach that the peptide is likely to be protected from degradation from extracellular proteases while bound to class I, and the construct taught by WO 96/04314 has peptides that are either bound or fused to class I MHC.

18. Claims 21-23 and 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/04314 (IDS reference) in view of Celluzzi *et al* (J. Exp. Med. 1/1996, Vol. 183, pages 283-287), Liu *et al* (J.Exp. Med. 1/1997, Vol. 185, No. 1, pages 165-170) and Utz *et al* (J. Virology, 2/1996, Vol. 70, No. 2, pages 843-851).

WO 96/04314 teaches an APC transfected with DNA encoding a multivalent fusion, *i.e.,* chimeric, protein comprising two full-length MHC class I molecules (heavy chain and β2m) or MHC class II molecules, each fused to the same antigenic peptide and an immunoglobulin chain, said immunoglobulin chain comprising a constant region, that causes the fusion protein product of the transfected DNA to be expressed on the cell surface, *i.e.,* the chimeric protein is "bound" to the surface of the cell, or can be GPI-linked to the surface of a cell, and use for *in vivo* administration. WO 96/04314 teaches that fusion proteins comprising the MHC class I molecules may comprise an immunoglobulin comprising a variable region. WO 96/04314 teaches the importance of a co-stimulatory molecule in eliciting an MHC class I-restricted CTL response. WO 96/04314 teaches assays to determine if an MHC/peptide combination is stimulating T cells, said assay comprising contacting T cells with APC that expresses the class I MHC complex (especially page 8 at lines 6-24, page 19 at lines 10-17, page 26 at lines 22-30, page 27 at lines 1-30, page 28 at lines 1-16, pages 29-30, paragraph spanning pages 31-32, page 39 at lines 14-21, page 40 at lines 18-27, page 41 at lines 5-15, page 42 at lines 4-16, claims 31 and 31).

WO 96/04314 does not teach wherein the cell capable of delivering a co-stimulatory signal is a dendritic cell, nor wherein the said cell is bound to the fusion protein via the variable region of the immunoglobulin portion of the protein. WO 96/04314 does not teach wherein the MHC molecule is HLA-A2, nor wherein the antigenic peptide is HTLV-1 tax 11-19.

Celluzzi *et al* teach that priming of CTL responses requires the presentation of the relevant antigen by professional antigen presenting cells (APCs) capable of providing co-stimulation, and that dendritic cells (DC) are efficient APCs for CTL induction and may be an attractive adjuvant for immunizations. Celluzzi *et al* teach that DC pulsed with antigen induce CTL-mediated response to the said antigen (especially first paragraph on page 283), and that such DC is advantageous over other forms of peptide delivery in that the peptide in preformed complexes with class I on the surface of the DC is likely to be presented in the appropriate APC context for T cell stimulation, and that the peptide will be protected from degradation by extracellular proteases (especially last sentence in column 1 on page 286). Celluzzi *et al* teach cell surface antigens on DC and detection of them using antibodies specific for said cell surface antigens (especially Preparation of DC section at column 2 on page 283).

Liu *et al* teach an IgG1 isotype monoclonal antibody 7D6 specific for the human dendritic cell marker CD21 (especially abstract and Materials and Methods section on page 166 at the second and third full paragraphs at column 1).

Utz *et al* teach in HLA-A2 positive individuals with HTLV-1 associated HAM/TSP, the vast majority of CD8+ HTLV-1 specific CTL recognize one viral epitope presented by HLA-A2, the immunodominant HTLV-1 tax 11-19 peptide (especially abstract and introduction sections). *Utz et al* teach detecting the presence of such CD8+ T cells using target cells transfected with HLA-A2 and pulsed with the tax 11-19 peptide (especially first section at column 1 on page 8450. Utz *et al* teach that it is not known if the virus-specific CTL are beneficial to the patient or contribute to the pathogenesis of the condition (especially second to last paragraph of article on page 850). Utz *et al* teach generation of the CTL by stimulating CD8+ cells from peripheral blood of patients with antigen pulsed PBL (Materials and Methods section, last paragraph, column 1 on page 844).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an MHC class I/peptide/IgG fusion protein as taught by WO 96/04314 using an IgG antibody comprising a variable region specific for a DC cell surface antigen such as taught by Celluzzi *et al* or of an IgG1 antibody as taught by Liu *et al*, and to have attached the fusion protein to a cell capable of delivering a co-stimulatory signal as taught by WO 96/04314, said cell being a DC taught by Celluzzi *et al*. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an MHC class I/viral peptide/IgG1 fusion protein using the tax 11-19 peptide and HLA-A2 taught by Utz *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to prepare a composition comprising said fusion protein attached to a cell capable of providing a co-stimulatory signal as taught by WO 96/04314 because Celluzzi *et al* teach that DC are capable of providing the requisite co-stimulatory signal, and further teach the advantage of using DC with peptide bound to MHC on their surface for immunization, and Liu *et al* teach a mouse IgG1 antibody specific for dendritic cells. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to do this because Celluzzi *et al* teach that the peptide is likely to be protected from degradation from extracellular proteases while bound to class I, and the construct taught by WO 96/04314 has peptides that are either bound or fused to class I MHC. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to prepare a standardized and stable source of APC that provide a strong co-stimulatory signal and the tax 11-19 peptide bound to HLA-A2 because WO 96/04314 teaches making a composition comprising APC with the MHC class I/antigenic peptide/IgG fusion protein bound to the cell surface, Utz *et al* teach generation of tax 11-19/HLA-A2 specific CTL from peripheral blood of HTLV-1 patients with HAM/TSP using PBL isolated from HLA-A2 positive patients and pulsed with tax 11-19 immunodominant peptide, and Liu *et al* teach an IgG1 antibody specific for human dendritic cell marker CD21. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to stimulate and expand CTL *in vitro* for further study since Utz *et al* teach that it is not known if virus-specific CTL are beneficial or

deleterious, and the combined references teach *in vitro* stimulation of T cells using immobilized fusion protein.

19. Claims 21-23 and 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,869,270 in view of Utz *et al* (J. Virology, 2/1996, Vol. 70, No. 2, pages 843-851) and Liu *et al* (J.Exp. Med. 1/1997, Vol. 185, No. 1, pages 165-170).

U.S. Patent No. 5,869,270 discloses MHC peptide complex/IgG fusion proteins comprising two MHC class I molecules (heavy chain and β2m), or MHC class II molecules, each fused to the same antigenic peptide and further comprising an immunoglobulin chain, that are expressed on the surface of APC that are dendritic cells by transfection of DNA encoding the said fusion proteins, *i.e.,* the proteins are "bound" to the cells, and the dendritic cells may be used to stimulate an immune response in humans or in animals (especially column 8, column 21 at lines 1-54, column 24, column 25 at lines 1-59).

U.S. Patent No. 5,869,270 does not disclose wherein the Ig is IgG1, nor wherein the MHC is HLA-A2, nor wherein the peptide is HTLV-1 tax 11-19.

Utz *et al* teach in HLA-A2 positive individuals with HTLV-1 associated HAM/TSP, the vast majority of CD8+ HTLV-1 specific CTL recognize one viral epitope presented by HLA-A2, the immunodominant HTLV-1 tax 11-19 peptide (especially abstract and introduction sections). *Utz et al* teach detecting the presence of such CD8+ T cells using target cells transfected with HLA-A2 and pulsed with the tax 11-19 peptide (especially first section at column 1 on page 8450. Utz *et al* teach that it is not known if the virus-specific CTL are beneficial to the patient or contribute to the pathogenesis of the condition (especially second to last paragraph of article on page 850). Utz *et al* teach generation of the CTL by stimulating CD8+ cells from peripheral blood of patients with antigen pulsed PBL (Materials and Methods section, last paragraph, column 1 on page 844).

Liu *et al* teach an IgG1 isotype mouse monoclonal antibody 7D6 specific for the human dendritic cell marker CD21 (especially abstract and Materials and Methods section on page 166 at the second and third full paragraphs at column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an MHC/ peptide/Ig fusion protein disclosed by U.S. Patent No. 5,869,270 using the tax 11-19 peptide and HLA-A2 taught by Utz *et al* and the IgG1 monoclonal antibody 7D6 taught by Liu *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to prepare a standardized, stable source of APC that provide a strong co-stimulatory signal and the tax 11-19 peptide bound to HLA-A2 because U.S. Patent No. 5,869,270 discloses making a composition comprising DC

APC with the MHC class I HLA-A/antigenic peptide/IgG fusion protein bound to the cell surface, and Utz *et al* teach generation of tax 11-19/HLA-A2 specific CTL from peripheral blood of HTLV-1 patients with HAM/TSP using PBL isolated from HLA-A2 positive patients and pulsed with tax 11-19 immunodominant peptide, by Liu *et al* teach a mouse monoclonal antibody specific for a dendritic cell marker. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to stimulate and expand CTL *in vitro* for further study since Utz *et al* teach that it is not known if virus-specific CTL are beneficial or deleterious, and the combined references teach *in vitro* stimulation of T cells using immobilized fusion protein.

20. The reference EP 0352761 A2 in the information disclosure statement filed 4/5/04 has not been considered because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of this patent listed that is not in the English language. See 37 CFR 1.98(a)(3).

21. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner /Group 1640/Technology Center 1600
December 20, 2005

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application No. 10/816,932	Applicant(s) Schneck et al	
	Examiner Marianne DiBrino	Art Unit 1644	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: There are no SEQ ID NO for the sequences appearing in figure 19 and figure 1B.

Applicant Must Provide:

☒ A~~n initial or~~ substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ A~~n initial or~~ substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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